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ORIGINAL ARTICLE

Efficacy and Risks of Therapeutic Hypothermia after Pediatric Cardiac Arrest: A Systematic Review

Anna Luíza Machado Nogueira,[1] Ana Luísa dos Santos Maciel,[1] Amanda Campos Querubino,[1] Roberta Teixeira Prado,[1] Jussara Regina Martins[1]

Faculdade de Ciências Médicas e da Saúde de Juiz de Fora,[1] Juiz de Fora, MG – Brazil

Abstract

Background: Therapeutic hypothermia is used in adults and neonates after cardiac arrest, but its efficiency in children under 18 years old is still uncertain.

Objective: To evaluate the effectiveness and risks of therapeutic hypothermia after cardiac arrest in children under 18 years of age through a systematic review.

Methods: A systematic review was performed in January 2022 in the MEDLINE, SciELO, Cochrane, and LILACS databases. Inclusion criteria: randomized controlled trials (RCTs) performed in humans. Articles from other typologies, published more than 10 years ago, or with volunteers over 18 years old were excluded.

Results: Four studies were identified, of which 3 were analyzed; all of them were of moderate quality according to the Jadad Scale and the Cochrane Collaboration tool. The studies indicated that lowering the temperature did not improve data on mortality and adverse events. Two studies did not identify statistically significant differences ($p > 0.05$) considering hypothermia in relation to normothermia in terms of survival, safety, and global neurobehavioral and cognitive function. The other study did not show improved serum biomarker concentrations.

Conclusions: The results found in this review do not support the use of therapeutic hypothermia after pediatric cardiac arrest, as this intervention did not provide any apparent benefits in terms of safety, adverse events, survival, and neurological impact. We recommend the conduction of new RCTs using the measurement of serum biomarkers to better evaluate the effectiveness of the intervention.

Keywords: Child; Heart Arrest, Induced; Hypothermia; Systematic Review; Meta-Analysis.

Introduction

Cardiac arrest (CA) in children offers high risks to survival, neurological function, and quality of life.[1] This condition compromises cerebral blood flow, damages neurons, and results in memory and concentration problems, cerebral palsy, seizures and, in extreme cases, vegetative state and death.[2]

CA causes ischemia and decreases oxygenation, producing cytotoxic edema due to cellular depolarization and the consequent influx of salt and water, extracellular accumulation of excitatory amino acids, and neuronal death. Therapeutic hypothermia (TH) is able to reduce neuronal metabolism, oxygen consumption, and cerebral blood flow, in addition to controlling depolarization and limiting cell death.[3-6]

TH is used in adults and neonates who have suffered CA, but it is not yet indicated for children in the same situation because the cause of arrest in each of these groups is different: in children, CA mainly results from respiratory problems, while in adults it is mostly due to heart disease. This leads to different injury patterns, making it impossible to generalize the effectiveness of TH in these cases.[1,2,7] Evidence indicates that this

Mailing Address: Anna Luíza Machado Nogueira
Faculdade de Ciências Médicas e da Saúde de Juiz de Fora. Alameda Salvaterra, 200. Postal Code: 36033-003, Salvaterra, Juiz de Fora, MG – Brazil.
E-mail: almachadonogueira@gmail.com

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intervention may have a neuroprotective effect, hence it is under research.[8]

The aim of this study thus was to verify, via a systematic review, the efficacy and risks of TH after CA in children under 18 years old.[9,10]

Methods

This systematic review was conducted based on the *Preferred Reporting Items for Systematic Review and Meta-Analysis* (PRISMA) methodology.[11]

Literature search strategy

The search and selection of studies happened between July 2020 and January 2022, without language restrictions. The Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed), Scientific Electronic Library Online (SciELO), Cochrane, and Latin American and Caribbean Literature in Health Sciences (LILACS) databases were used in our search. The following descriptors and their synonyms, according to the Medical Subject Headings (MeSH), were used in the search phrase: "hypothermia, induced," "heart arrest," and "child."

Item 4 of the PRISMA methodology refers to the PICO (patient/population, intervention, comparison, outcomes) strategy to guide systematic reviews, and it is presented in Chart 1.[11]

Inclusion and exclusion criteria

Aiming at the scientific value of the analyzed studies, only randomized controlled trials (RCTs) were selected. Inclusion criteria were: studies with humans that investigated the use of TH after CA in people under 18 years old (using the MEDLINE filters "infant," "preschool child," "child," and "adolescent"). Other types of articles, published more than 10 years ago, with volunteers aged 18 years or older, not directly related to the subject, and duplicates of articles found in more than one database were excluded.

Data extraction

The articles found with the search phrase were analyzed by two independent researchers in the following stages: 1) title analysis; 2) abstract analysis; 3) full article reading when the abstract was related to the topic or when the reading was not sufficient to define its eligibility. Divergences were solved by a third independent author.

Assessment of the quality of information and risk of bias

Two independent authors used the Jadad scale and the Cochrane Collaboration tool for randomized clinical trials to assess the quality of information and risk of bias.[12,13] The Jadad scale assesses whether the research was adequately randomized and described as double-blind, identifying sample losses and exclusions to quantify study quality[12]. On the other hand, the Cochrane risk-of-bias tool for randomized trials assesses risks involving allocation, selection, outcome analysis, and other biases.[13]

Results

Characteristics of the selected studies

Using our search phrase, 446 studies were identified in the databases. When applying the inclusion and exclusion criteria, 22 studies were obtained. After reading the full texts and eliminating those that were not directly related to the topic or that were secondary analyses of the studies

Chart 1 – PICO strategy used in this study.

Participants: people under 18 years old who suffered CA
Interventions: TH
Comparison: TN; TH during 24 or 72 h.
Outcomes: mortality; adverse events; survival **after** 12 months; survival with favorable functional status ; neurobehavioral function; global cognitive function; safety; serum biomarker concentrations; unfavorable outcome.
Study design: RCT.

CA: cardiac arrest; TH: therapeutic hypothermia; TN: therapeutic normothermia; RCT: randomized controlled trial.

by Moler et al.[7] and Moler et al.,[9] 3 studies were selected, as shown in Figure 1.[7,9,10]

Sample characteristics

The selected studies comprised a sample of 658 patients under 18 years old, without gender restrictions[7,9,10]. Table 1 summarizes the general characteristics of the included publications.

Analyzed variables

The 3 selected studies assessed mortality and adverse events. Studies 1 and 2 measured survival rates and survival with favorable neurobehavioral outcomes (Vineland Adaptive Behavior Scale, Second Edition – VABS ≥ 70) 1 year after CA. In addition, the impact on neurobehavior and overall cognitive function were analyzed separately.[7,9] Study 3, on the other hand, showed serum concentrations of biomarkers, unfavorable outcomes, and compared the duration of TH interventions (24 h or 72 h). Table 2 presents the main results.[10]

Main tools used in the analyzed studies

The VABS-II scale assesses the impacts of CA on neurobehavioral function by analyzing deficiencies in adaptive behavior and development, in addition to motor, communication, socialization, and daily life skills (self-care, personal hygiene, and feeding).[14]

In studies 1 and 2, when VABS-II could not be applied, the Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores were used for sample selection[7,9]. In order to be eligible, children should score 1 (good overall performance) or 2 (mild disability) on these scales. Study 3 used PCPC to identify cases of unfavorable outcomes.[13] Both POPC and PCPC are based on the Glasgow scale[15] and quantify the morbidity of patients after critical conditions. While

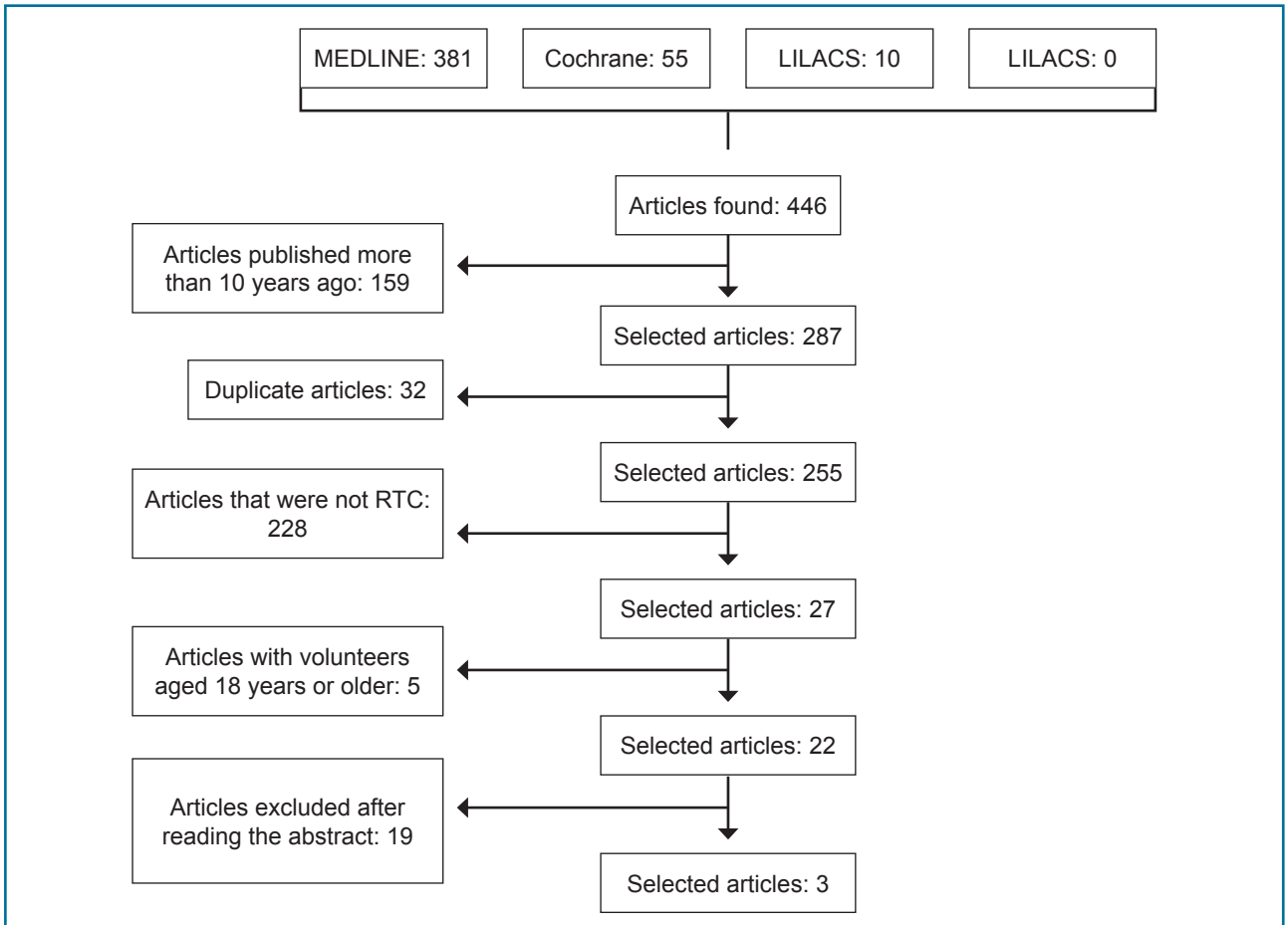

Figure 1 – Flowchart of the study selection process.

Table 1 – General characteristics of the studies included in this systematic review

	1	2	3
Author	Moler FW et al., 2017[7]	Moler FW et at., 2015 [9]	Fink EL et al., 2018[10]
Sample	329	295	34
Inclusion criteria	People aged from 48 h to 18 years, in a coma after in-hospital CA, who received compressions for at least 2 minutes, and dependent on mechanical ventilation.	People aged from 48 h to 18 years, in a coma after out-of-hospital CA, who received compressions for at least 2 minutes, and dependent on mechanical ventilation.	People aged from 7 days to 17 years, who were hospitalized in a coma in the ICU after in- or out-of-hospital CA.
Exclusion criteria	Glasgow motor response subscale = 5 or 6, inability to randomize 6 h after return of circulation, severe active and refractory bleeding, preexisting disease associated with life expectancy < 12 months, and clinical decision to suspend aggressive treatment.	Inability to randomize 6 h after return of circulation, Glasgow motor response subscale = 5 or 6, clinical decision to suspend aggressive treatment, and traumas associated with CA.	Do not resuscitate status, pregnancy, contraindication for MRI, other acute brain diseases, brain death, metabolic diseases that affect the brain, active bleeding, or coagulation defects.
Intervention	166 patients were treated with TH (33.0 ºC) and 163, with TN (36.8 ºC), for 120 h. All of them were pharmacologically paralyzed and sedated. TN patients had their temperature maintained at 36.8 ºC, whereas TH patients were kept at 33.0 ºC for 48 h and were then reheated for 16 h or more until they reached 36.8 ºC.	155 patients were treated with TH (33.0 ºC) and 140, with TN (36.8 ºC), for 120 h. All of them were pharmacologically paralyzed and sedated. TN patients had their temperature maintained at 36.8 ºC, and TH patients were maintained at 33.0 ºC for 48 h and were then reheated for 16 h or more until they reached 36.8 ºC.	17 patients were treated with TH (33 ± 1 ºC) for 24 h, and 17 were treated with TH for 72 h. All of them were treated with a cooling blanket, which was reheated at 0.5 ºC every 4 h until reaching 37 ºC.

CA: cardiac arrest; ICU: intensive care unit; MRI: magnetic resonance imaging; TH: therapeutic hypothermia; TN: therapeutic normothermia.

POPC classifies functional morbidity, PCPC evaluates cognitive disorders.[16]

The Wechsler Abbreviated Scale of Intelligence (WASI) and the Mullen Scales of Early Learning were used to analyze global cognitive function. The WASI is applied to people aged from 6 to 89 years and investigates aspects such as verbal knowledge, visual information processing, spatial and non-verbal reasoning, and fluid and crystallized intelligence through the evaluation of vocabulary, block design, similarities, and matrix reasoning.[17] The Mullen Scales are applied to children aged 68 months or older and is used to analyze data such as visual perception, expression, and receptive language, as well as fine and gross motor skills.[18]

Methods used by the studies

This review focused only on RCTs, and studies 1 and 2 are considered references on the subject.[7,9] These used the same method and duration of intervention (120 h): volunteers were sedated, paralyzed, and had their central temperatures monitored at 2 sites (esophageal, rectal, or bladder) using the automatic mode of the temperature control unit. Temperature management was conducted in 2 stages: initially, central temperature was maintained at 33 ºC for 48 h using blankets, which were later reheated for 16 h or more up to 36.8 ºC.[7,9]

The other RCT analyzed in this review used a similar intervention, but with different temperature management: it was kept at 33 ± 1 ºC for 24 h or 72 h, then patients were reheated by 0.5 ºC every 4 h up to 37 ºC.[10]

Quality and risk of bias

Table 3 shows the Jadad scale, used for evaluating study quality, and the Cochrane Collaboration tool,

Table 2 – Main results of the studies included in this systematic review

	1	2	3
Mortality	Up to the 28th day HG 59 (37%) x NG 66 (41%) p = 0.4	Up to the 28th day HG 87 (57%) x NG 93 (67%) p = 0.08	Up to the sixth month HG-24h 8 (47%) x NG-72h 4 (24%)
Adverse events	Hypokalemia, seizures, requirement for renal replacement therapy, thrombocytopenia	Hypokalemia, hyperglycemia, seizures, requirement for renal replacement therapy, thrombocytopenia	Infection, seizures, bleeding, rearrest
Survival after 12 months	HG 81 (49%) x NG 74 (46%) p = 0.45	HG 57 (38%) x NG 39 (29%) p = 0.13	-
Survival with favorable functional status	GH 48 (36%) x GN 48 (39%) p = 0.63	GH 27 (20%) x GN 15 (12%) p = 0.14	-
Unfavorable outcome	-	-	No differences between groups
Neurobehavioral function	p = 0.7	p = 0.13	-
Global cognitive function	p > 0.05	p > 0.05	-
Safety	Occurrences of infection, serious bleeding, and arrhythmias within 7 days were similar between groups	Occurrences of infection, serious bleeding, and arrhythmias within 7 days were similar between groups	-
Serum biomarker concentrations	-	-	Higher on HG-24h, but p < 0.05

HG: hypothermia group, NG: normothermia group, CA: cardiac arrest, p > 0.05 = nº statistically significant differences between groups.

employed in the analysis of risk of bias.[12,13] All studies scored a 3 (moderate quality) on the Jadad scale, as they were not described as double-blind. As for the Cochrane tool, the aspect with the highest risk of bias in the 3 studies was the blinding of participants, but other variables still presented uncertain risks.

Discussion

Evidence from studies 1 and 2 indicates that TH was not more effective than TN for a better prognosis of children and teenagers after CA both in and out of hospital.[7,9] In-hospital CA had better outcomes, since its numbers of survivors and favorable functional results were higher.[7]

The results of the third study suggest some advantages, considering the levels of serum biomarkers when using TH for 72 h compared to 24 h. No significant differences were identified in the occurrence of adverse events between groups.[10]

Mortality

In articles 1 and 2, mortality was evaluated after 28 days, and in study 3, after 6 months. None of the studies found a statistically significant difference between groups, thus TH in the 120-, 24-, and 72-h regimens had no significant effects on mortality in people under 18 years old after CA.[7,9,10] It is worth mentioning that differences in confidence intervals for this variable can weaken the comparison between findings.

Adverse events

Hypothermia did not significantly alter the occurrence of adverse events, and its duration (24 or 72 h) did not influence this outcome. Seizures were a frequent adverse effect reported in all 3 studies. The main adverse effects are mentioned in Table 2 and these findings are compatible with those of a meta-analysis that showed that TH may be related to changes in coagulation, neurological function, and serum ion concentrations.[1]

Table 3 – Classification of articles according to quality and risk of bias.

Modified Jadad scale	Article 1	Article 2	Article 3
Was the study described as randomized?	Yes	Yes	Yes
Was the study described as double-blind?	No	No	No
Was there a description of exclusions and losses?	Yes	Yes	Yes
Has the method for generating the randomization sequence been described and appropriate?	Yes	Yes	Yes
Was the double-blind method described and appropriate?	No	No	No
Final score	3	3	3
Cochrane Collaboration tool	**Article 1**	**Article 2**	**Article 3**
Generation of random sequence	Low	Low	Low
Allocation concealment	Uncertain	Uncertain	Low
Blinding of participants and professionals	High	High	High
Blinding of outcome evaluators	Uncertain	Uncertain	Uncertain
Incomplete outcomes	Low	Low	Low
Selective outcome report	Uncertain	Uncertain	Uncertain
Other sources of bias	Low	Low	Low

Survival at 12 months

Articles 1 and 2 concluded that there was no significant difference between groups in terms of survival one year after CA,[7,9,19-25] so it is not possible to state that TH was able to increase 12-month survival.

Secondary analyses of this evidence point to some risk factors such as: children under 1 year old, serum lactate concentrations ≥ 10 mmol / L, the use of more than 4 doses of adrenaline, and chest compressions performed for more than 30 minutes.[21,34] Patients who had CA during the weekends or caused by a condition that threatens life or sudden unexpected death also had lower survival rates as a consequence of prolonged exposure to the absence of blood flow.[21]

Other risk factors for survival are preexisting health conditions and the requirement for renal replacement therapy. Renal impairment before or after CA decreases survival rates by intensifying electrolyte and blood pH changes caused by the arrest.[24,25]

Protective factors are: administration of low doses of adrenaline, heart rate before CA with ventricular tachycardia and ventricular fibrillation, cardiac etiology, CA occurring during the week and the day, and in-hospital CA. Patients who had in-hospital CA were twice as likely to survive when compared to those who had out-of-hospital CA.[21,22]

Survival with favorable neurobehavior

Articles 1 and 2 defined survival with favorable neurobehavior as scoring at least 70 points on the VASB II scale in the first year after CA. Both studies reported that there was no statistically significant difference between groups.[7,9,19-22,24-26]

Secondary analyses suggest some risk factors: children under 1 year old or 5–12 years old, CA caused by a life-threatening condition or by sudden unexpected infant death , low blood pH and platelet count, serum lactate concentrations ≥ 10 mmol / L, and obesity.[21,22]

Factors such as CA , the administration of a lower dose of adrenaline, and underweight children were listed as protective. In-hospital CA was considered a protective factor, and patients with this condition were 3 times more likely to survive with favorable neurobehavior when compared to those who had out-of-hospital arrests.[21,22] Obesity influences this variable because it compromises the precision of the concentration of drugs administered for resuscitation

and the correct energy for defibrillation, which require the patient's weight for their calculations. In addition, the quality of cardiopulmonary resuscitation is affected in obese patients.[21]

It is thus not possible to state that TH was effective in guaranteeing a good neurobehavioral outcome in 1-year CA survivors, as it is not the only factor that influences survival with favorable neurobehavior.

Adverse outcome

An adverse outcome was established by article 3 as a PCPC score of 4, 5, or 6, or an increase > 1. Eleven children in the 24-h TH group (65%) and 10 in the 72-h TH group (59%) had an adverse outcome, with no difference between groups 6 months later. It is noteworthy that S100b levels were increased in participants who underwent 24-h therapy before this change could have a direct relationship with the intervention. Since these levels are linked to brain damage , it cannot be said that the interventions were the sole responsible for the observed results.[10]

While studies 1 and 2 prioritized the use of VABS-II, study 3 used exclusively PCPC to analyze the impact of TH on neurobehavioral outcome, impairing the analysis of this variable.

Neurobehavioral evaluation

A neurobehavioral evaluation was performed in studies 1 and 2, based on the difference between VABS-II right after CA and 1 year after the intervention.[7,9] Patients with good results had a difference in VABS ≥ 15.[9,23] Those who died and those who obtained the lowest possible score in VABS-II were classified as having the worst results.[9,22]

The change between baseline scores and scores after 12 months and the difference of less than 15 points were similar between groups in both studies.[9,19,22,27-30] Drowning was related to less negative impacts, while respiratory etiologies aggravated the condition.[29]

Advanced age and high initial VABS-II were related to worse results. According to a secondary analysis, this may be due to the inability of young children to perform the activities measured by the test, causing their initial score to be reduced and the decline after 12 months to be smaller, making the deficit less evident when compared to older children.[29]

The evidence indicates that TH was not beneficial in fighting brain damage from hypoxemia. Intrinsic factors, however, can change VABS-II results, but they do not reflect cognitive deficits themselves.

Global cognitive function

Global cognitive function was rated in studies 1 and 2 using the Early Learning Composite score from the Mullen Scales of Early Learning, the IQ scored at the WASI, and the combined Mullen and Wechsler tests . The WASI was used in participants aged 6 years or older and the Mullen scales, in children under 6 years old. The results did not differ between groups.[7,9]

Secondary analyses investigated the impairment of specific skills due to ischemic injury to identify individual demands in the rehabilitation and education of children and teenagers after CA. Those most affected were: executive function, fine motor skills, visuomotor skills, and visual memory. On the other hand, the IQ did not change significantly.[27-30]

Younger children do not have these areas fully developed, so deficiencies may be less noticeable, whereas in older children these changes are easily identified and closely linked to the sites that are most sensitive to hypoxic injury.[27] One of the evaluations by VABS-II aimed to discover which cognitive deficits the child already had before the arrest, reporting the effectiveness of the intervention more accurately.[27]

Studies have not indicated a protective effect of TH on global cognitive function, and the analysis of the impact of this intervention was compromised by the influence of age and preexisting conditions.

Safety

In studies 1 and 2, the incidence of infection, the need for blood products, and the occurrence of severe arrhythmias 7 days after randomization were analyzed as safety measures. The incidence rates of these parameters were similar in both groups.[7,10,19,20,22]

It can thus be inferred that TH in the 120-h regimen can be considered a safe intervention, since it did not expose patients to a higher risk of complications when compared to the TN group.

Biomarker concentration

Study 3 evaluated the serum concentrations of biomarkers such as neuron specific enolase (NSE), S100b, and myelin basic protein (MBP). Three mL

of blood were collected by a blinded technician for treatment and results, twice a day (every 12 h) for 4 days, and once on the seventh day after spontaneous return of circulation.[10]

These biomarkers assist in the prediction of therapeutic characteristics and neurological prognosis, also helping in the choice of treatment.[10,31] Neuronal injuries and worse results were concluded to be related to higher serum concentrations of NSE and S100b.[10]

The concentrations of all biomarkers were higher in the 24-h group, except for MBP on day 7, and baseline concentrations were similar in both arms. It is worth mentioning that S100b was increased in the 24-h group in the 12-h to 24-h period, and it is not possible to state that this difference was due to the intervention.[10]

Researchers advise that these measurements should be validated for clinical use in pediatric CA, as they complement clinical results and help guide care. Moreover, these concentrations should be inclusion criteria in neuroprotective therapy trials or be used to optimize their duration.[10]

Although considered efficient in the analysis of neurological injuries, the measurement of these biomarkers has been little addressed in studies on the subject. In this context, more RCTs should be performed associating these biomarkers with clinical aspects to validate them as instruments for assessing TH on post-CA neurological outcomes.

Limitations

Limitations of this study involve the analysis of studies with different methodologies and tools for assessing neurobehavioral state and the impossibility of blinding researchers.

It is worth mentioning that the benefits of TH cannot be totally denied by the observed results, as some statistical data showed confidence intervals that contemplated 1. Therefore, the intervention may or not be a protective factor, requiring further studies with larger samples and longer follow-up periods to reach more definitive results.

In addition, studies had some specific limitations: article 1 was interrupted because of the difficulty in obtaining an adequate sample size, associated with minor benefits. Furthermore, the delay in reaching the desired temperature delayed the return of circulation, which may have caused adverse effects. Study 2 postponed the evaluations of patients with hypothermia, which may cause a false idea of greater survival rates after the intervention. In article 3, a small sample size was used, and the PCPC was not blindly applied.[7,9,10]

Conclusions

There was no apparent benefit of TH compared to TN after pediatric CA regarding its efficacy and risk prevention, thus it is not possible to recommend this intervention. Other RCTs, involving larger samples, similar tools, and exploring the measurement of serum biomarkers, are necessary to assess this intervention.

Author contributions

Conception and design of the research: Nogueira ALM, Maciel ALS, Querubino AC, Prado RT, Martins JR. Acquisition of data: Nogueira ALM, Maciel ALS, Querubino AC. Analysis and interpretation of the data: Nogueira ALM, Maciel ALS, Querubino AC. Writing of the manuscript: Nogueira ALM, Maciel ALS, Querubino AC. Critical revision of the manuscript for intellectual content: Prado RT, Martins JR.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Study association

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Ethical approval and consent

This article does not contain any studies with human participants or animals performed by any of the authors.

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